

## Trophoblast stem cells.

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### Public Summary:

During the early stages of embryogenesis, the first developmental decision occurs. The small collection of cells that will give rise to the embryo (and eventually to the baby) are sequestered inside at one end of the spherical embryo. The cells that will give rise to the placenta, which are termed trophoblasts, move to the outer surface of the sphere. Even at this very early stage these placental cells show a remarkable degree of specialization. For example, by 5 to 6 days of human development, they must be able to attach the embryo to the uterine surface, subsequently burying the conceptus deep within its wall. Thus, the establishment of pregnancy critically depends on generation of the stem cells that will go on to form the placenta. Subsequently, the entire course of the pregnancy is determined by the ability of placental stem cells to form the differentiated cell types that comprise this temporary but vital organ. This is due to the placenta's many critical functions. They include rerouting the flow of maternal blood to the placenta, which carries out the exchange functions of the lungs, digestive system and kidneys before birth. One of the most unusual placental functions is shielding the offspring from maternal immunological attack, the norm for foreign transplants such as the offspring, which is a compilation of both the mother and the father. Therefore, its correct function is vital to the normal growth and development of the offspring. Conversely, we know that many major pregnancy complications are associated with abnormal placental development. Preeclampsia, the sudden onset of high blood pressure in the mother, is a prime example. Thus, understanding placentation has important implications for human health. The placenta has a complement of stem cells with restricted developmental potential such that under normal circumstances they contribute only to this organ. This arrangement is a very common developmental theme. Normal growth before birth requires these stem cells to make exact copies of themselves, which expands the pool for later differentiation into the mature cell types that carry out the critical functions of any organ. This paper presents an overview of the mechanisms that are involved the allocation and differentiation of placental stem cells. It is interesting to note that unlike other organs and tissues, placental structure significantly diverges among species. Scientists think that the unique features of the human placenta evolved to maximize blood flow to the offspring, which was required for the development of our comparatively larger brains. In this context, mechanisms that are shared among animal models and humans are thought to be important because they have been conserved. In this context, we reviewed the origin of placental stems cells. We also summarized what is known about the neighborhood in which they are found. The so-called niche is a very important regulator of stem cell behavior as external signals can modify the decision to self-renew or differentiate. Finally, we summarized information about the molecular networks that control assumption of placental identity and, later on, promote differentiation.

### Scientific Abstract:

Trophoblast stem cells (TSC) are the precursors of the differentiated cells of the placenta. In the mouse, TSC can be derived from outgrowths of either blastocyst polar trophectoderm (TE) or extraembryonic ectoderm (ExE), which originates from polar TE after implantation. The mouse TSC niche appears to be located within the ExE adjacent to the epiblast, on which it depends for essential growth factors, but whether this cellular architecture is the same in other species remains to be determined. Mouse TSC self-renewal can be sustained by culture on mitotically inactivated feeder cells, which provide one or more factors related to the NODAL pathway, and a medium supplemented with FGF4, heparin, and fetal bovine serum. Repression of the gene network that maintains pluripotency and emergence of the transcription factor pathways that specify a trophoblast (TR) fate enables TSC derivation in vitro and placental formation in vivo. Disrupting the pluripotent network of embryonic stem cells (ESC) causes them to default to a TR ground state. Pluripotent cells that have acquired sublethal chromosomal alterations may be sequestered into TR for similar reasons. The transition from ESC to TSC, which appears to be unidirectional, reveals important aspects of initial fate decisions in mice. TSC have yet to be derived from domestic species in which remarkable TR growth precedes embryogenesis. Recent derivation of TSC from blastocysts of

the rhesus monkey suggests that isolation of the human equivalents may be possible and will reveal the extent to which mechanisms uncovered by using animal models are true in our own species.

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